Optimization of Factor Settings for Pharmaceutical Filling Process by Factorial Design of Mixed Levels

Guangming Chen[1], Andrew Ezekiel[2], and Tridip Bardhan[1]

[1]Department of Industrial and Systems Engineering,
Morgan State University, Baltimore, Maryland, USA

[2]Digene Corporation,
Gaithersburg, Maryland, USA

Corresponding author's Email: guangming.chen@morgan.edu

Author Note: Dr. Guangming Chen is a Professor and Graduate Coordinator in the Department of Industrial and Systems Engineering at Morgan State University. He also serves as the Director of Systems Engineering and Management Institute (SEMI) in the School of Engineering at Morgan State University. Professor Chen's research interest involves Systems Engineering, Robust Design, and Quality Control & Reliability.

Dr. Andrew Ezekiel received his Doctor of Engineering degree from the Department of Industrial and Systems Engineering (ISE) at Morgan State University in 2007. After he received his doctoral degree, he joined Digene Corporation as a senior quality engineer. He has served the company since then.

Dr. Tridip K. Bardhan is currently serving as the Chairman of the Industrial and Systems Engineering (ISE) Department at Morgan State University. He is also serving as the Director of the Manufacturing Process Laboratory (MPL) under the ISE Department. He received his undergraduate, master's and doctorate degrees in Industrial Engineering from Wichita State University. Dr. Bardhan's work and research experience involves a wide range from industries, government agencies, and national laboratories.

Abstract: Variations in products and processes can be costly to manufacturers in terms of the loss for rework, scrap, and inspection. This paper studied the variability of a generic pharmaceutical filling process by the analysis of the fill weight and the related four factors. Firstly, we used mixed-level factorial design to perform the experiments and collect the data. The significance of the process factors and their interactions was determined by using analysis of variance (ANOVA). Next, process capability analysis and optimization process were conducted. The ultimate goal of the study was to develop the optimal level settings of controllable factors to minimize the quality loss caused by the deviation of process mean from the target value (nominal fill weight). The optimal level settings of the process factors were obtained for high and low viscosity products. As discussed in the paper, significant quality improvement in the filling process can be achieved by reducing the variation in fill weights. The methodology in this paper may be generalized to other similar filling processes.

Keywords: Factorial Design, Optimization, Pharmaceutical Process, Process Capability, Quality Improvement, Variation Reduction.

1. Introduction

Pharmaceutical manufacturers are regulated to ensure their process to meet fill weight specifications for liquid bottle medicine. The filling process must perform consistently over time to meet this requirement. A filling machine dispenses the product into containers. The medicine's weight in each container must meet or exceed a specified label claim weight. Under-filled containers put the company at risk of liability due to FDA regulations (e.g., companies may face a recall or a serious fine). Hence, pharmaceutical companies tend to set the process mean much higher than the target value to reduce the risk of producing under-filled units and ensure better conformance to specifications. However, due to the high cost of medicine, using a higher process mean or over-filled strategy results in substantial loss to the manufacturer (Tan 1990). Therefore, a pharmaceutical company must find the optimal level settings for the controllable input variables that can optimize the process mean (i.e., make the process mean equal to or as close as possible to the target value) while minimizing the variability in the fill weight.

The variations of fill weight can be caused by the design of the filling process, skills of operators, workplace environment, machine parameters, and the physical properties of the product (Usher et al. 1996; Taylor 1991). Sampling plan, control charts, regression analysis, and experimental design are typical tools for quality improvement of filling processes. These statistical tools are also used to identify sources of fill weight variations, determine the optimal process mean (Anis 2003; Misiorek and Barnett 2000), and reduce the process variability. Earlier researchers in this area included Burr (1949), Springer (1951), and Bettes (1962). They considered the problem of determining the optimal process mean with specified upper and lower specification limits while taking economic aspects into consideration, and thus to reduce the total cost. Nelson (1978; 1979) found an appropriate function for a better approximate optimal solution with a plot of errors, and then extended Burr's work by developing a graphical method to select the optimal settings. Hunter and Kartha (1977) developed a model to determine the optimal target value of an industrial process to minimize the expected loss by assuming that all under-filled items are sold at a fixed price. A generalization of this model was reported by Bisgaard, Hunter, and Pallesen (1984), who developed a procedure for selecting the optimal value for the process mean, considering a situation that under-filled items are sold for a price that is proportional to the amount of ingredients in the container.

We studied the problem of determining the factor settings that optimize the process mean (e.g., reduce the deviation of the average fill from the target value) as well as minimize the variability in a pharmaceutical filling operation. A 4^1x2^3 mixed level factorial design approach was used to design the experiments. For more details about mixed level factorial design, see Wu and Humada (2000) and Montgomery (2005). ANOVA test of the General Linear Model procedure available in the Design-Expert software package was used to analyze the significance of the factors and their interactions. In the final stage of the analysis of the data, we used Design-Expert to predict the optimal factor settings, or to obtain the best level combination of controllable factors for both high and low viscosity products. Significant improvement was observed in terms of minimizing the deviation of the average fill from the target value and reducing the variability around the process mean. For reasons of confidentiality and protection of proprietary information of the company, as set in an agreement with the company before conducting this project, all data in this study were coded.

2. Model of Filling Process and Related Factors

As illustrated in Fig. 1, the factors affecting the filling process of a pharmaceutical product line include signal factors, control factors, and uncontrolled noise factors. A control variable is the one that manufacturer can control, and as a result, it may alter the amount used in the product or process design. The **control factors** or variables are as follows:

- *Line speed:* The line speed is a quantitative parameter. It is defined as the number of bottles filled per minute (bpm). The line speed is a control factor. It was adjusted several times during a pilot study to learn the settings that impact fill weight variation.
- *Height of solution in the filler bowl (HSFB):* Adjusting the float bar and a sensor mounted on top of the filler bowl controls the amount of product in the filler bowl. The quantity of product in the filler bowl affects the pressure in the filler. Two levels can be assigned to this factor (high and low).
- *Production Shift:* Operator skills, setup, over or under adjustments (improper fill head adjustments) and running damaged nozzle could affect the fill weight.

Signal Factors: A special factor, with a range of settings, which is controlled by the user of the product to make use of its intended function. It is used in dynamic experiments (Chen and Kapur 1997). An example of a signal factor in this research is viscosity. Product viscosity is the resistance of fluids to flow (i.e., the thickness of the liquid). Viscosity is determined by the nature of the product (medicine). Viscosity tests are performed on some batches during in-process and finished product.

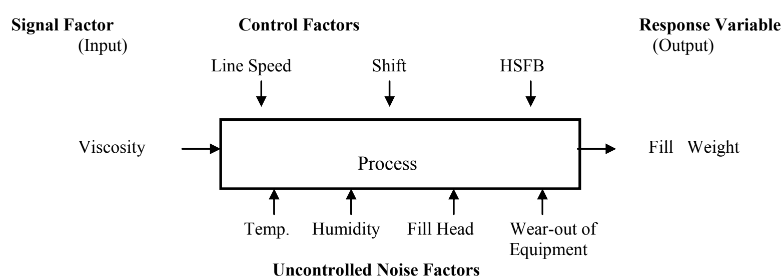

Figure 1. Schematic Model of the Filling Process

Table 1. Control and Signal Factors and Their Levels for Mixed Level Factorial (4^1x 2^3) Design

Coded levels	Line Speed, bpm (x_1)	Viscosity, cps (x_2)	Shift (x_3)	HSFB (x_4)
1	50	10-200	1	Low
2	65	>200	2	High
3	80			
4	94			

Noise factors that we could not control in this research include:

- *Environment change:* These include such factors as temperature and room humidity. During the manufacturing process of a batch, the temperature of the jacket surrounding the mixer is controlled by the presence of cooling water running through the mixer jacket, if desired. Otherwise, the mixer runs at the ambient temperature. Temperature is treated as a noise factor in our study.
- *Fill heads*: There are 21 fill heads that can fill bottles simultaneously on the rotary fill machine. These fill heads may have variations in valve leakage as well as inner diameter and other dimensions due to usage.
- *Wear-out of equipment:* This, of course, occurs because of equipment usage.

In Fig. 1, the uncontrolled noise factors are: fill heads (21 fill heads or filling stations on a rotary filling machine), wear and tear of equipment, changes in the packaging environment (such as changes in temperature and humidity).

Based on brainstorming and group discussion of company employees involved in the specific process, three control factors and one signal factor were chosen for the optimal level settings for the filling process to minimize the process variation and the mean deviation from the target.

In this study, we used a 4^1x2^3 mixed level factorial design to accommodate the restriction of production line set-up. One factor has 4 levels and three other factors have 2 levels each. As shown in Table 1, there are four different levels that are assigned to line speed, while viscosity, shift, and the height of solution in the filler bowl (HSFB) have two levels each.

2.1 Statistical Model of the Filing Process

A full factorial design of these level combinations resulted in 32 experimental conditions (experimental runs). If interactions of three or more factors are assumed negligible, the statistical model of the characteristic of the filling process is given by (Montgomery 2005):

$$y_{ijklm} = \mu + \tau_i + \beta_j + (\tau\beta)_{ij} + \gamma_k + (\tau\gamma)_{ik} + (\beta\gamma)_{jk} + \delta_l + (\tau\delta)_{il} + (\beta\delta)_{il} + (\gamma\delta)_{kl} + \varepsilon_{ijklm} \quad (1)$$

Where i = 1, 2, 3, 4; j, k, l = 1 or 2 and m = 1, 2, … 21; Also,

y_{ijklm} represents an observed fill weight at specific level setting of process parameters
μ represents the overall mean of the filling process
τ_i represents the effect of the *i*th level of line speed
β_j represents the effect of the *j*th level of product viscosity
γ_k represents the effect of the *k*th level of production shift
δ_l represents the effect of lth level of HSFB
ε_{ijklm} represents the random error
$(\tau\beta)_{ij}$, $(\tau\gamma)_{ik}$, $(\beta\gamma)_{jk}$, $(\tau\delta)_{il}$, $(\beta\delta)_{il}$, and $(\gamma\delta)_{kl}$ are the interaction effects of respective factors.

2.2 Quality Loss Evaluation of the Filling Process

To evaluate the loss to the company due to the deviation from the target value, Taguchi's loss function can be used and the expected quality loss is given by:

$$E[L(y)] = k[\sigma^2 + (\bar{y} - T)^2] \quad (2)$$

where L(y) is the loss caused by a deviation from the target measure T of a product quality characteristic y; $\bar{y}$ is the mean of y; and k is a numerical constant transferring the quadratic value of the deviation to a monetary scale. Originated from the concept of expected quality loss, C_{pm}, defined as $(USL-LSL)/6[\sigma^2+(\bar{y}-T)^2]^{1/2}$ or $C_P/[1+(\bar{y}-T)^2/\sigma^2]^{1/2}$ for symmetric cases, can be used, where USL and LSL are upper specification limit and lower specification limit respectively; C_P is the potential process capability ratio. For asymmetric cases such as in this study, C_{pkm}, based on the actual process capability ratio C_{PK}, can reflect the actual process capability:

$$C_{pkm} = \frac{C_{pk}}{\sqrt{1 + \left(\frac{\bar{y} - T}{\sigma}\right)^2}} \tag{3}$$

To evaluate the quality loss to the company before quality improvement, we used the following data (coded) obtained during the packaging operation for product *A*. Given: LSL = −5.3, T = −1.9, USL = 6.2, σ^2 = 2.5308, Mean = 3.1381, k can be obtained as 0.06 if the company's scrap cost is $2.00 per unit. Using Eq. 2, the expected quality loss is E[L(y)]=$1.67 per unit on average. Figure 2 shows the process capability chart for the filling process of product *A*. From the chart, it can be observed that the mean of the process is centered at 3.1381, and not on the target value. The standard deviation is 1.5909. The histogram extends beyond the upper specification limit. This implies that some units were filled above the upper specification limit. Any deviation from the target incurs a loss. C_{pk}=0.70 is much lower than the desired minimum value 1.33. Additionally, C_{pm} (C_{pkm})=0.21 indicates the process center is far away from the target, which presents an opportunity for quality improvement.

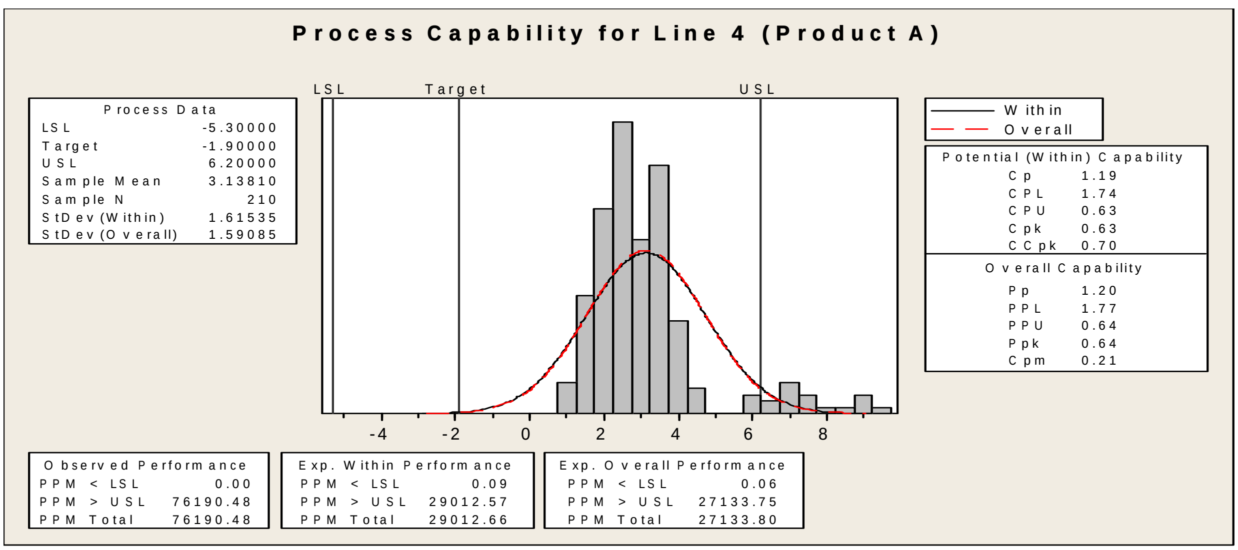

Figure 2: Process Capability Chart for the Filling Process of Product- A.

3. Experiments and Data Collection

The mixed level design worksheet in Table 2 was generated with the Minitab software package. The worksheet depicts a single four-level factor and three two-level factors that we intended to study. Although the number of levels for the factors is different, as shown in Table 1, it can be seen from Table 2 that the four-level factor "line speed" is proportionately balanced. We used the design worksheet for the mixed level experimental run. The process factors are displayed in columns 5 through 8 in Table 2.

Table 2: Design Worksheet in Standard Order for Mixed Level Factorial Design

Std. Order	Run Order	Center Point	Blocks	Line Speed Levels	Viscosity Levels	Shift	HSFB
5	1	1	1	1	2	1	1
6	2	1	1	1	2	1	2
8	3	1	1	1	2	2	2
10	4	1	1	2	1	1	2
16	5	1	1	2	2	2	2
11	6	1	1	2	1	2	1
21	7	1	1	3	2	1	1
4	8	1	1	1	1	2	2
2	9	1	1	1	1	1	2
26	10	1	1	4	1	1	2
18	11	1	1	3	1	1	2
30	12	1	1	4	2	1	2
9	13	1	1	2	1	1	1
14	14	1	1	2	2	1	2
23	15	1	1	3	2	2	1
3	16	1	1	1	1	2	1
29	17	1	1	4	2	1	1
12	18	1	1	2	1	2	2
28	19	1	1	4	1	2	2
15	20	1	1	2	2	2	1
7	21	1	1	1	2	2	1
13	22	1	1	2	2	1	1
19	23	1	1	3	1	2	1
25	24	1	1	4	1	1	1
22	25	1	1	3	2	1	2
20	26	1	1	3	1	2	2
27	27	1	1	4	1	2	1
17	28	1	1	3	1	1	1
24	29	1	1	3	2	2	2
32	30	1	1	4	2	2	2
31	31	1	1	4	2	2	1
1	32	1	1	1	1	1	1

The four factors are carried forward from Table 1 to Table 2, and this specifies 32 runs for the design. The following approach was used for this experiment. The production line was set up according to the level of each factor shown in Table 2. For instance, for the first row of Table 2, the entry in column 5 is 1, the entry in column 6 is 2, the entry in column 7 is 1, and the entry in column 8 is also 1; therefore, run 1 has: line speed (x_1) at level 1, viscosity (x_2) at level 2, shift (x_3) at level 1, and HSFB (x_4) at level 1.

Table 3: Fill Weight Obtained from Mixed Level Factorial Experiments

Fill Head	Sample Numbers				
	1	2	…	31	32
1	78.1	78.1		78.1	78.5
2	77.6	77.1		78	77.8
3	78.1	77.8		78.4	78.1
4	77.8	74.1		78.4	78.1
5	78.4	77.9		78.4	78.4
6	78	77.7		78.5	78.2
7	76.2	77.8	…	77.7	78.1
8	78	77.8		77.6	78.4
9	76.3	77.9		76.2	78.2
10	75.5	77.7		76.1	78.3
11	78.6	77.8		77.8	78.2
12	77.8	78.2		77.6	78.5
13	78.2	77.4		78.6	78.4
14	78.5	77.6		78.5	78.3
15	78.1	78		78.4	78.5
16	78.3	78.8	…	78.5	78.4
17	78.8	78.3		78.7	78.5
18	78.6	77.8		78.6	78.4
19	79	78.3		77.7	78.3
20	77.5	77.8		78	78.1
21	77.4	77.7		78.4	78.3

The data were collected in steady state operating conditions. Because the filling machine contains 21 fill heads, we collected 21 samples from each filling cycle (1 unit from each fill head) during each experimental run. We collected 672 samples (21 samples in 32 experimental runs) from the experimental runs. We were able to collect so many samples because weighing the samples was not destructive and repetitions of the data under the same condition usually provide more accuracy in later analysis. Table 3 shows a proportion of the fill weights of the 32 runs or factor level combinations specified in Table 2. The complete data is available from the corresponding author.

4. Statistical Analysis and Interpretation of Results

At the completion of the experiments, we analyzed the collected data using the Design-Expert software package and then drew conclusions from the analysis. Fig. 3 shows that line speed and HSFB have positive effects; that is, increasing these variables increases the average fill. However, line speed has a nonlinear effect. As the line speed goes from 80 to 94 bpm, the averages fill drops.

Fig. 4 shows cube plots of average fill weight and standard deviation obtained from the mixed factorial design experiment for the factors of line speed and shift. From the plot, we can see that the maximum standard deviation occurs at the corner point for shift 1, line speed 94 bpm for a high-viscosity product (point A in Fig. 4), and the minimum standard deviation occurs when line speed is 50 bpm and shift is 1 for low-viscosity product (point B in Fig. 4). Thus, for both low and high viscosity products, running the filling process at low line speed on shift 1 produces the minimum variability in the filling process.

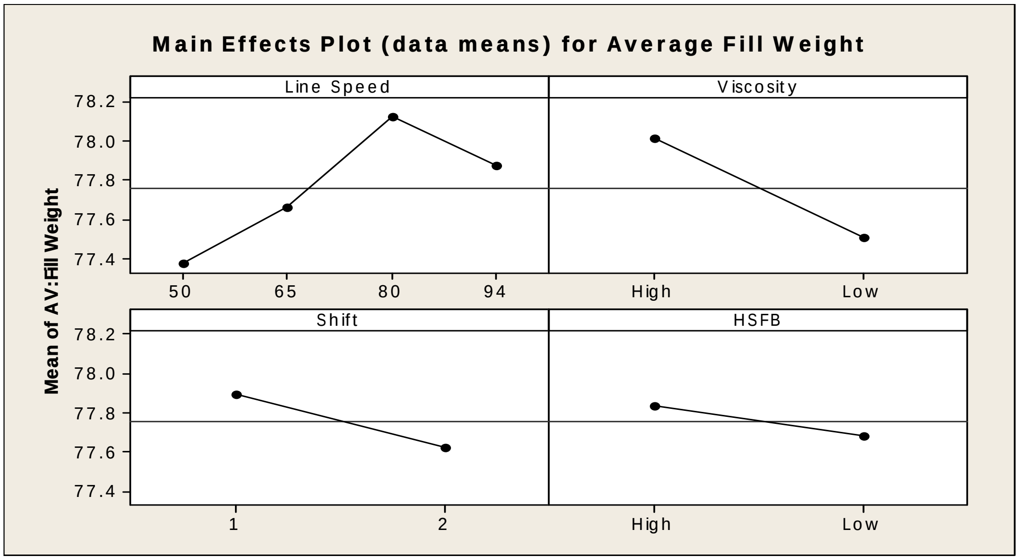

Figure 3: Main Effects Plot of Mean Response

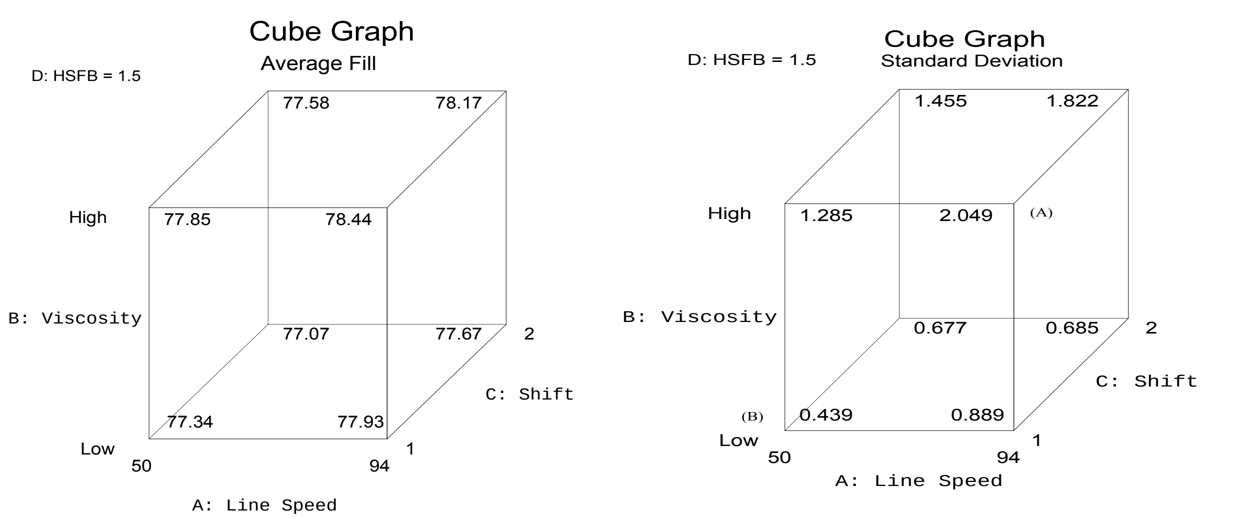

Figure 4: Cube Plots for Mean Response (left panel) and Standard Deviations (right panel).

Fig. 5 is a graphical representation of response surface and contour plots for the average fill as a function of line speed and viscosity while both HSFB and shift are fixed at level 2. These plots were obtained from the fitted model (for response surface, see Shah et al. (2004) and Zhu et al. (2007)). From both plots, it can be observed that the average fill increases as line speed increases.

In addition to these plots, we fit the models (using Design-Expert) for the response *y* and standard deviation of the data obtained during the mixed level factorial experiment (See Eqs. 4 and 5). The models include linear and two-factor interaction terms. The quadratic, cubic, and higher interaction terms are aliases (Table 4). The fitted model can be used to predict the individual response for various levels settings.

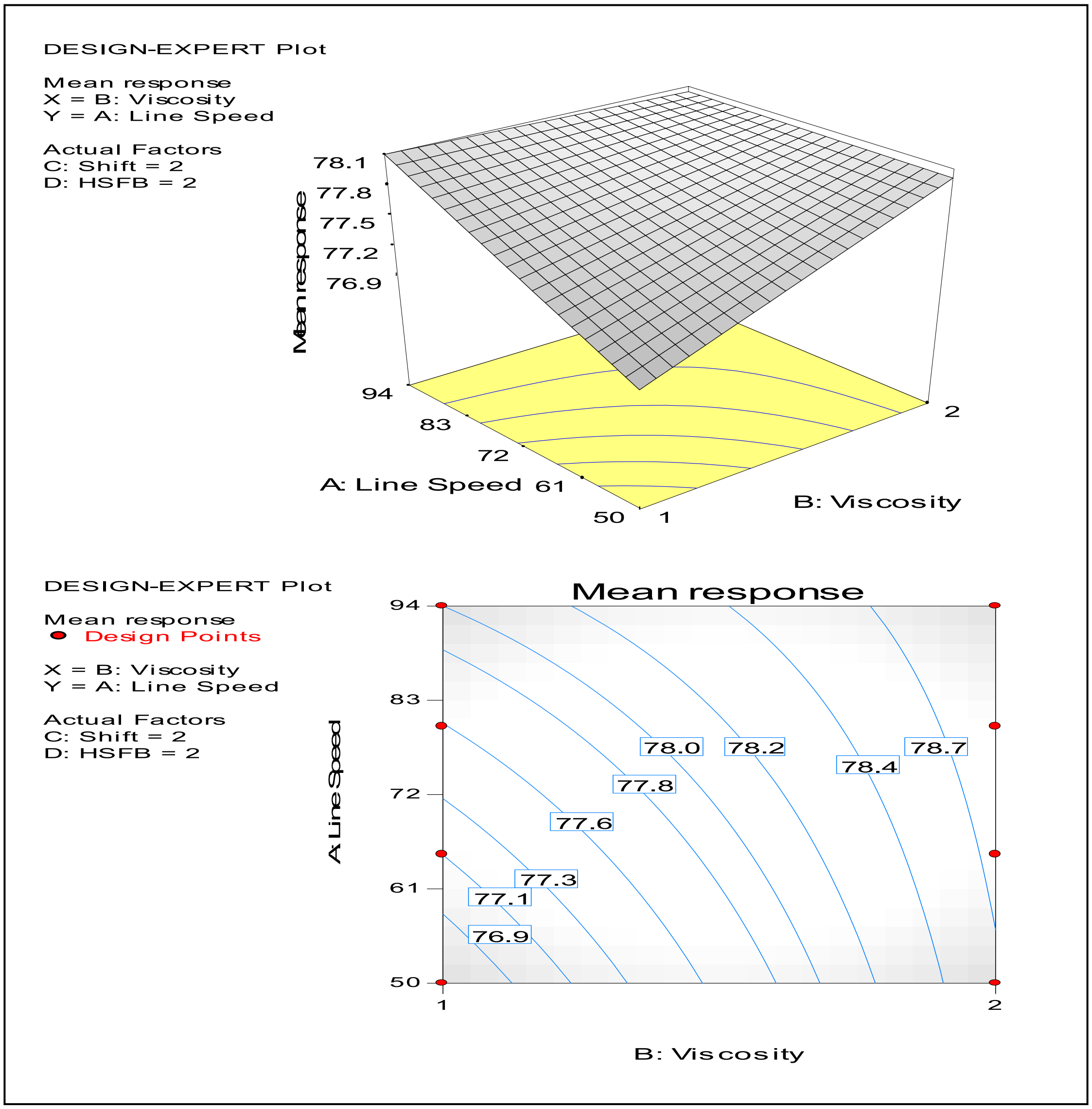

Figure 5: Response Surface Plot (upper panel) and Corresponding Contour Plot (lower panel).

Process mean, $\hat{y} = 81.4962 + 0.0386x_1 - 0.3740x_2 - 3.0357x_3 - 4.4761x_4 - 0.0257x_1x_2 - 0.0089x_1x_3 + 0.0179x_1x_4 + 0.9375x_2x_3 + 0.8875x_2x_4 + 1.3375x_3x_4$ (4)

Variance, $\sigma^2 = 6.47 - 0.0848x_1 - 0.5570x_2 - 1.34x_3 - 5.03x_4 + 0.0354x_1x_2 - 0.0098x_1x_3 + 0.0502x_1x_4 + 0.0574x_2x_3 + 0.239x_2x_4 + 1.32x_3x_4$ (5)

Where, x_1 : Line Speed
x_2 : Viscosity

x_3 : Shift
x_4 : HSFB

The x_1x_2, x_1x_3, x_1x_4, x_2x_3, x_2x_4, and x_3x_4 terms are the interactions, which ignore quadratic and higher-order interaction terms.

4.1 ANOVA for the Mixed Level Factorial Experiment

The Design-Expert software package was also used to analyze the data from the mixed level factorial experiment using the desirability function approach. Table 4 depicts the ANOVA table obtained for the average fill weight versus the variables (line speed, HSFB, shift, and viscosity). The desirability approach was used to find the operating conditions for the most desirable response value, i.e., the response with the minimum deviation from the target value. We obtained the optimal parameter settings for both low and high viscosity products from the table. As shown in Table 4, solution 1 has the highest overall desirability for both high and low viscosity products. Table 5 gives the optimal parameter settings for low and high viscosity products depicted in Table 4.

4.2 Confirmatory Runs

Table 4: Computer Ooutput from Design-Expert for Fitting a Model to the Data in Table 3.

Response: Mean response
Sequential Model Sum of Squares

Source	Sum of Squares	DF	Mean Square	F Value		Prob > F
Mean	1.935E+005	1	1.935E+005			Suggested
Linear	4.40	4	1.10	1.34	0.2808	
2FI	9.21	6	1.53	2.48	0.0565	Suggested
Quadratic	0.53	1	0.53	0.85	0.3670	Aliased
Cubic	5.24	8	0.66	1.09	0.4293	Aliased
Residual	7.20	12	0.60			
Total	1.935E+005	32	6047.35			

Desirability tests

Solutions Number	Line Speed	Viscosity	Shift	HSFB	Mean response	Desirability	
1	**94**	**2**	**1**	**2**	**78.2**	**0.929**	**Selected**
2	94	2	1	2	78.2	0.920	
3	94	2	1	1	78.2	0.918	
4	89	2	1	2	78.1	0.917	
5	94	2	1	2	78.2	0.909	
6	90	2	1	2	78.2	0.902	
7	94	2	1	1	78.1	0.896	
8	80	2	1	2	78.0	0.883	
9	77	2	1	2	77.8	0.820	

9 Solutions found

Constraints

Solutions Number	Line Speed	Viscosity	Shift	HSFB	Mean response	Desirability	
1	**80**	**1**	**2**	**2**	**78.0**	**0.923**	**Selected**
2	80	1	2	2	78.1	0.923	
3	94	1	2	2	78.1	0.922	
4	94	1	2	2	78.1	0.922	
5	94	1	1	2	78.2	0.921	
6	80	1	1	1	78.0	0.920	
7	94	1	1	1	78.1	0.919	
8	80	1	1	2	77.9	0.918	
9	94	1	1	2	78.2	0.911	
10	94	1	1	1	78.3	0.902	

10 Solutions found

To verify the optimal parameter settings as predicted by the Design-Expert software package, confirmatory experiments (using the optimal factor settings given in Table 5) were performed. Two hundred and ten samples were taken from each of the confirmatory runs. Tables 6 and 7 display the collected data. The result of the confirmation test shows a good match between the predicted and actual fill weights (Figs. 6 and 7).

Fig. 6 is a capability chart derived from confirmatory setting 1, using the treatment combination of factor levels given in Table 5. The figure indicates that the filling process performed extremely well during the confirmatory trial, producing a C_{pk} of 2.14 and a standard deviation of 0.51791. The chart shows that the process mean is on target.

Fig. 7 is a capability chart derived from confirmatory setting 2, using the optimal treatment combination of factor level given in Table 5. The figure indicates an improvement in the filling process during the confirmatory run, producing a C_{pk} of 2.17 and a standard deviation of 0.71743. The chart shows that the process mean is very close to the target. Compared with the original process capability shown in Fig. 2, a significant quality improvement in terms of process capability can be achieved for both confirmation runs.

Table 5: Recommended Optimal Factor Settings

Setting	Viscosity	Line speed	HSFB	Shift
1	1	80 bpm	2	2
2	2	94 bpm	2	1

Table 6: Fill Weights Obtained from Confirmatory Run for Setting-1.

Fill Head	Sample #									
	1	2	3	4	5	6	7	8	9	10
1	75.5	75.7	75.8	75.7	75.7	75.4	75.4	74.8	75.7	74.7
2	76.5	76.5	76.2	76.3	75.7	76	75.8	75.5	75.4	75.4
3	76.8	76.7	76.3	76.0	76.6	76.4	76.0	75.4	75.2	75.7
4	76.9	76.9	77.0	77.1	75.9	76.6	76.1	76.1	75.9	76.6
5	76.1	76.1	76.7	76.3	75.5	76.0	75.7	75.6	76.0	75.4
6	75.6	76.0	75.9	76.0	75.9	75.7	75.9	75.6	75.6	75.1
7	75.9	76.0	76.2	75.9	75.0	75.5	75.5	75.9	75.5	75.8
8	76.0	76.6	76.1	76.1	76.0	76.3	75.5	76.0	76.0	76.2
9	75.4	75.8	75.5	76.2	75.8	75.7	75.4	75.5	74.7	75.3
10	76.2	76.3	76.2	75.9	76.0	75.8	75.4	75.4	75.5	75.9
11	78.7	76.8	76.8	76.4	75.8	76.2	76.1	75.4	75.5	76.6
12	76.7	76.2	76.7	76.1	76.0	76.0	75.6	75.7	75.2	75.7
13	76.4	76.3	76.9	75.9	75.5	76.1	76.3	75.5	75.4	76.0
14	75.8	75.4	76.1	75.9	76.0	75.9	75.3	74.7	74.7	75.4
15	76.7	76.6	76.9	76.6	76.7	76.3	76.3	76.0	75.4	76.4
16	75.9	76.1	75.8	75.6	75.2	75.9	75.8	75.4	75.4	75.3
17	75.4	76.0	76.1	76.5	75.6	76.1	75.4	75.7	75.5	75.6
18	76.2	76.6	76.4	75.9	76.1	75.8	75.4	75.3	75.5	75.5
19	76.0	76.2	76.1	76.7	75.8	76.0	75.4	75.4	76.1	76.2
20	76.5	76.8	76.4	76.4	75.6	75.9	76.0	75.4	75.4	75.9
21	75.8	76.6	76.4	76.9	75.7	76.3	75.9	76.0	75.7	75.4

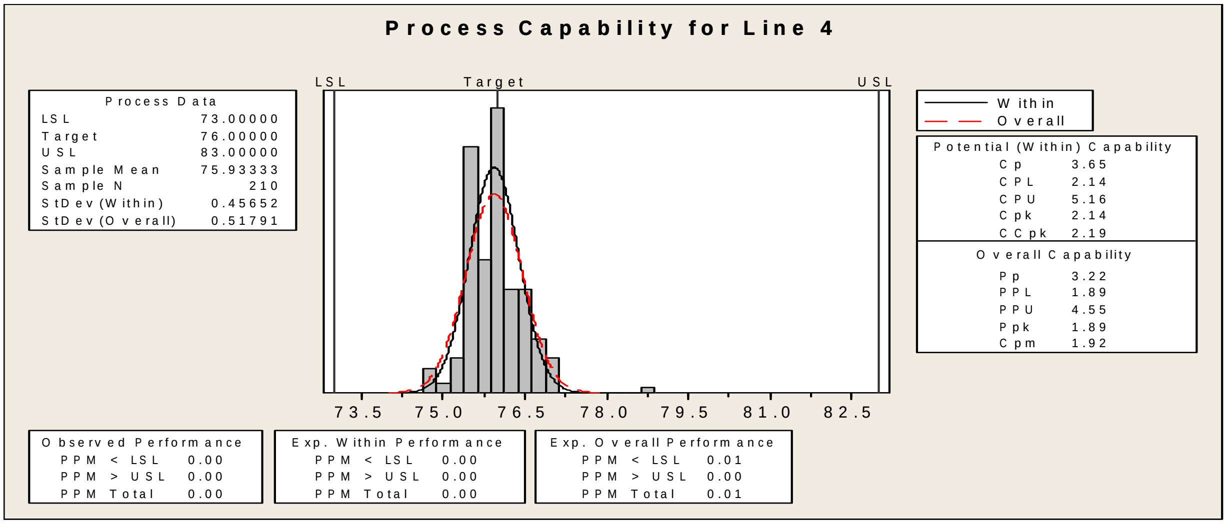

Figure 6: Process Capability Chart from Confirmatory Run for Setting-1.

Table 7: Fill Weights Obtained from Confirmatory Run for Setting-2.

Fill Head	Sample #									
	1	2	3	4	5	6	7	8	9	10
1	77.2	77.0	77.8	77.3	76.4	76.0	77.7	77.3	77.6	77.3
2	77.1	77.1	76.6	77.6	77.8	76.7	77.4	76.8	77.4	77.5
3	76.8	76.1	77.6	76.4	78.1	76.1	78.0	77.6	76.3	77.1
4	76.3	76.3	77.4	77.8	76.1	77.2	76.5	77.9	78.0	76.1
5	76.8	77.0	76.6	76.7	76.2	77.2	77.0	76.3	76.2	78.0
6	77.3	77.0	76.9	78.3	77.8	77.0	76.3	76.1	77.8	76.9
7	76.2	76.3	76.4	76.5	75.8	75.9	76.3	76.3	75.8	76.2
8	77.8	77.5	77.6	77.8	77.9	78.1	76.2	76.1	76.4	77.2
9	76.5	76.4	76.2	76.0	76.0	76.5	76.4	76.2	76.5	76.5
10	74.7	75.5	75.5	75.3	75.6	75.3	75.2	75.7	76.1	75.9
11	76.0	77.8	77.4	78.4	78.0	76.3	76.9	76.7	77.3	78.0
12	77.0	76.1	77.8	77.5	77.0	78.1	76.9	77.6	77.5	77.6
13	77.4	76.1	76.3	78.1	76.1	76.0	78.1	78.0	78.3	77.2
14	77.1	77.6	76.6	76.0	77.3	76.2	77.8	76.8	77.5	77.8
15	77.0	77.2	76.8	78.1	77.5	76.4	76.9	77.1	78.3	77.4
16	76.7	76.2	77.3	77.4	76.3	76.0	77.5	76.0	77.5	76.4
17	76.7	76.7	77.2	77.1	77.0	77.0	76.4	77.2	77.8	77.0
18	76.2	77.7	76.3	77.0	77.8	76.7	76.8	78.1	76.7	76.7
19	77.3	76.0	76.7	77.1	76.8	77.0	77.1	78.1	76.8	77.1
20	77.5	76.4	77.3	77.2	77.2	77.4	76.5	76.1	77.2	77.0
21	76.2	77.0	77.5	77.2	77.4	76.4	77.4	76.9	77.6	76.5

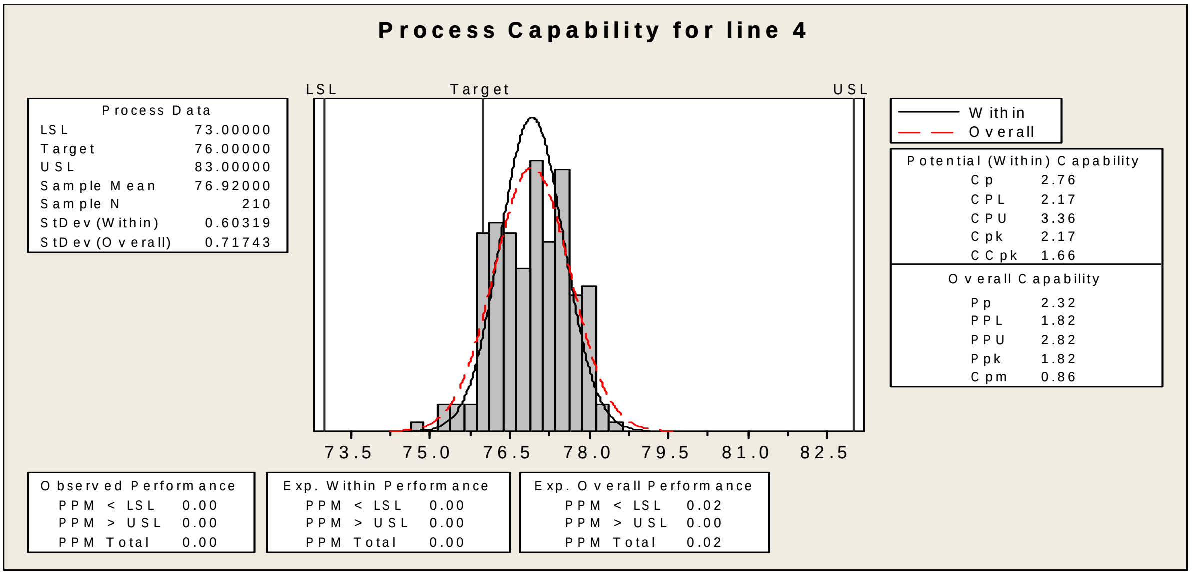

Figure 7: Process Capability Chart Derived from the Confirmatory Run for Setting-2.

5. Conclusion

This paper used the mixed level factorial design to study the pharmaceutical filling process and find the optimal process parameter settings. Quality loss function and process capability analysis were used to evaluate the current variability of a generic pharmaceutical filling process. The significance of the impact of the process factors and their interactions were determined through ANOVA based on a 4^1x2^3 mixed level factorial design. This mixed level factorial design of 32 experimental runs was performed, and Design-Expert software package was utilized to obtain the levels for controllable factor settings, as shown in Table 5, which optimizes the process for both high and low viscosity products. The confirmatory runs indicate a good match between the predicted results given by the regression model and the actual runs.

6. References

Anis, M. Z. (2003). Determination of the best mean fill. *Quality Engineering*, 15(3), 407-409.

Bettes, D.C. (1962). Finding an optimum target value in relation to fixed lower limit and an arbitrary upper limit. *Applied Statistics*, 11, 202-210.

Bisgaard, S., Hunter, W. G. and Pallesen, L. (1984). Economic selection of quality of manufactured product. *Technometrics*, 26(1), 9-18.

Burr, I. W. (1949). A new method of approving a machine or process setting, Part 1. *Industrial Quality Control*, 5, 12-18; Part 2, *Industrial Quality Control*, 6, 13-16.

Chen, G and Kapur, K.C. (1997). A two-step robust design procedure of linear dynamic system for reducing performance variations. *International Journal of Reliability, Quality and Safety Engineering*. 4(2), 119-131.

Hunter, W. G. and Kartha, C. D. (1977). Determining the most profitable target value for a production process. *Journal of Quality Technology*, 9(4), 176-181.

Misiorek, V. I., and Barnett, N. S. (2000). Mean Selection for Filling Processes under Weights and Measures Requirements. *Journal of Quality Technology*, 32, 111-121.

Montgomery, D C. (2005). *Design and Analysis of Experiments*, *6th Edition*, John Wiley & Sons, Inc.

Nelson, L. S. (1978). Best target value for production process. *Journal of Quality Technology*, 10, 88-89,

Nelson, L. S. (1979). Monograph for setting process to minimize scrap cost, *Journal of Quality* Technology, 11, 48-49

Shah, H K., Montgomery, D. C. and Carlyle, W. M. (2004). Response Surface Modeling and Optimization in Multi-response Experiments Using Seemingly Unrelated Regression. *Quality Engineering*, 16(3), 387-398.

Springer, C. H. (1951). A method of determining the most economic position of a process mean. *Industrial Quality Control*, 8(1), 36-39.

Tan, S. B. (1990). Influence of compression setting ratio on capsule fills weight and weight variability. *International Journal of Pharmaceutics*. 66, 273-282.

Taylor, W. A. (1991). *Optimization and Variation Reduction in Quality*. McGraw-Hill.

Usher, J. S., Alexander, S. M., and Duggines, D.C. (1996). The filling problem revisited. *Quality Engineering*, 9(1), 35-44.

Wu, C. F. J. and Humada, M. (2000). *Experments: Planning, Analysis, and Parameter Design Optimization*. John Wiley & Sons.

Zhu S., Lee S., Hargrove., K., Chen G. (2007). Prediction of Combustion Efficiency of Chicken Litter Using an Artificial Neural Network Approach. *Fuel,* 86(5-6), 877-886.